CASE REPORT

Unusual Visualization of an Adrenal Carcinoma on NP-59 Scintiscan

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[Iodine-131]6-beta-iodomethylnorcholesterol (NP-59) visualization of adrenocortical carcinoma is unusual. We describe a 17-year-old female with virilization and elevated plasma testosterone, dehydroepiandrosterone sulfate (DHEAS) and aldosterone. Magnetic resonance imaging disclosed a 9-cm right adrenal mass. NP-59 adrenal scanning displayed unilateral uptake of tracer and no visualization of the contralateral adrenal gland. Exploratory laparotomy revealed adrenocortical carcinoma. Subsequent immunohistochemical studies confirmed that the tumor was capable of producing a mixture of steroids, including testosterone, DHEAS and aldosterone. Visualization of an adrenal tumor on NP-59 scintiscan is an unusual finding, which cannot exclude the possibility of malignancy. [*J Formos Med Assoc* 2006;105(4):340–345]

Key Words: adrenocortical carcinoma, NP-59 scan, virilization

Adrenocortical carcinoma (ACC) is a rare disorder, with an estimated incidence of 0.6–2.0 cases per million.[1] In general, approximately half of these tumors are functioning, that is, secreting excess hormones and producing endocrinologic symptoms and signs, which lead to their discovery.[2] Among functioning ACCs, the most common hormonal abnormality is hypersecretion of both glucocorticoids and androgens (42%), followed by hypersecretion of glucocorticoids alone (41%) and hypersecretion of androgens alone (10%).[3] The prognosis of ACC is usually poor, and the life expectancy of afflicted patients depends largely on correct diagnosis leading to prompt treatment.[2]

Several diagnostic methods have been introduced to determine whether an adrenal mass is benign or malignant. NP-59 ([I-131]6-beta-iodomethylnorcholesterol) nuclear scintigraphy, a noninvasive diagnostic modality that can provide information about the functional status of the adrenal glands, has been utilized for this purpose. On NP-59 scintigraphy, benign adrenal adenomas typically exhibit a concordant imaging pattern, with uptake of the radiotracer on the side of the known adrenal mass and lack of visualization of the contralateral gland.[4,5] However, ACCs are usually not visualized, as the amount of radiotracer uptake by these tumors is usually insufficient to permit adequate imaging.[6]

In this report, we describe a virilizing ACC, which displayed a concordant imaging pattern on NP-59 scintigraphy. This tumor was found to be capable of producing dehydroepiandrosterone sulfate (DHEAS), testosterone and aldosterone both *in vivo* and *in vitro*.

Case Report

A 17-year-old female was referred for evaluation of primary amenorrhea. She had been a good ath-

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lete since childhood and had no major medical disorders. On physical examination, she was tall and lean, with clinical evidence of virilism, including hirsutism of the face and back, clitoromegaly, and deep voice. Breast development was Tanner stage 1 and Cushingoid features were not evident. Blood pressure was 100/65 mmHg. Biochemical data were within normal limits and serum potassium was 4.7 mmol/L (normal, 3.4–4.7 mmol/L).

Endocrine tests revealed a plasma estradiol level of 110 pg/mL (normal, 25–120 pg/mL), follicle-stimulating hormone (FSH) of 1.81 mIU/mL (normal, 5–30 mIU/mL), luteinizing hormone (LH) of 15.72 mIU/mL (normal, 2–200 mIU/mL), and prolactin of 7.87 ng/mL (normal, 3.0–26.0 ng/mL). Serum testosterone and DHEAS were both far above the detection limit of our laboratory (testosterone > 14.40 ng/mL, normal, 0.09–0.86 ng/mL; DHEAS > 1105 μg/dL, normal, 40–394 μg/dL). Serum aldosterone was also elevated (579 pg/mL; normal, 37.5–240 pg/mL), but plasma renin level was normal (13.21 pg/mL; normal, 2.5–21.4 pg/mL). Early morning cortisol was 6.4 μg/dL (normal, 5–25 μg/dL), which increased to 31.3 μg/dL 60 minutes after an intravenous injection of 250 μg of adrenocorticotropic hormone (ACTH)-(1-24) (Synacthen; Novartis Pharma AG, Basle, Switzerland). Serum 17-hydroxyprogesterone level was 4.73 ng/mL, which increased to 8.64 ng/mL 60 minutes after intravenous 250 μg ACTH-(1-24), thereby excluding the possibility of attenuated congenital adrenal hyperplasia.

Magnetic resonance imaging of the adrenal glands showed an oval-shaped multicystic tumor, 9 × 5 × 8.4 cm in size, in the right suprarenal region. The tumor showed low signal intensity on T1-weighted scan, and mild enhancement on T2-weighted scan (Figure 1). On dexamethasone-modified NP-59 adrenal scintiscan, mildly increased activity in the right suprarenal area was noted at 48 hours, and significant accumulation of tracer together with complete lack of visualization of the contralateral gland was noted at 72 hours (Figure 2), favoring a concordant pattern of tumor imaging.

Exploratory laparotomy was performed with removal of the right adrenal tumor. Pathologic examination of the resected tumor confirmed ACC. The postoperative course was uneventful, and replacement of hydrocortisone was not required. Six days postoperatively, plasma testosterone had decreased to 0.21 ng/mL, plasma aldosterone to 306

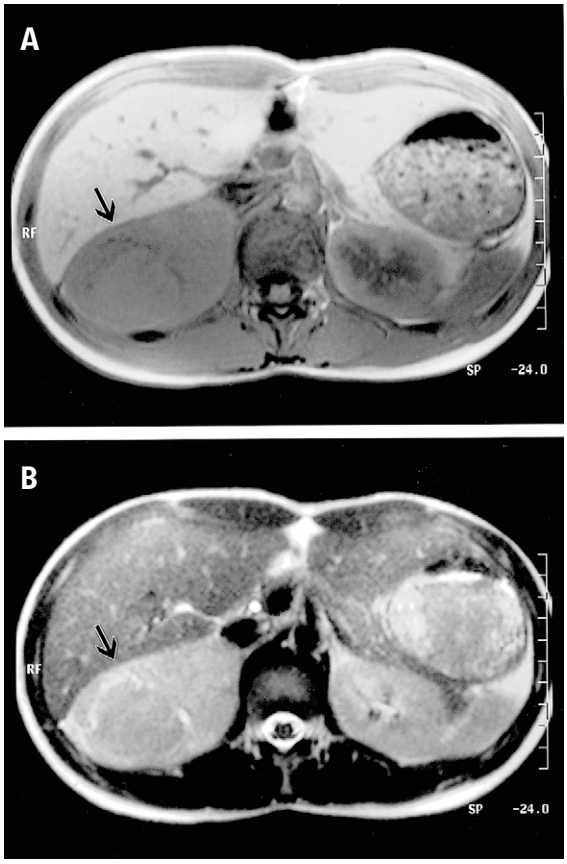

Figure 1. Magnetic resonance imaging of the adrenal glands shows an oval-shaped multicystic tumor, 9 × 5 × 8.4 cm in size, in the right suprarenal region. The tumor shows: (A) low signal intensity on T1-weighted scan (arrow); and (B) mild enhancement on T2-weighted scan (arrow).

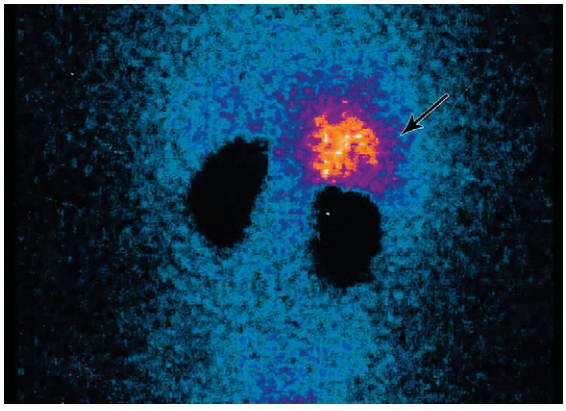

Figure 2. Dexamethasone-modified NP-59 adrenal scintiscan shows unilateral uptake by the tumor (arrow) and complete lack of visualization of the contralateral adrenal gland (posterior view).

pg/mL, and morning serum cortisol was 27.9 μg/dL (plasma DHEAS not available). Treatment with mitotane, 500 mg three times a day, was started 1 week after surgery and continued thereafter. One month after surgery, the patient experienced menarche, and her menstrual periods were subsequently regular. At the 1-year follow-up, she was apparently healthy and hirsutism was much improved. There was no clinical evidence of metastasis. Hormone profiles were all within normal ranges (testosterone, 0.65 ng/mL; DHEAS, 200 μg/dL; aldosterone, 128 pg/mL).

Histopathologic examination

The resected adrenal tumor measured 11 × 10 × 5 cm and weighed 265 g. Microscopic examination showed pleomorphic tumor cells, containing hyperchromatic bizarre nuclei and intensely eosinophilic cytoplasm (Figure 3). The tumor exhibited three pathologic features of the Weiss criteria:[7] high nuclear grade; > 75% eosinophilic cytoplasm; and diffuse architecture of tumor structure. It was, therefore, classified as an ACC.

Immunohistochemical staining was performed using the labeled streptavidin-biotin method (LSAB 2 Kit; DAKO Corp, Carpinteria, CA, USA). Antibodies were diluted as follows: aldosterone (1:50; Biogenesis, Poole, Dorset, UK); testosterone (1:25; Biogenesis); and DHEAS (1:30; BiosPacific, Emeryville, CA, USA). On microscopic examination, the tumor showed focal immunoreactivity (about 10%) to aldosterone. Well-stained cells tended to be arranged in thin trabeculae or ribbon patterns, and their nuclei were vesicular and uniform in size, whereas weakly-stained cells grew in sheets or in a pleomorphic sarcoma-like pattern (Figure 4A). In contrast to aldosterone, immunoreactivity to both testosterone and DHEAS was diffuse and intense throughout the whole specimen (Figures 4B and 4C).

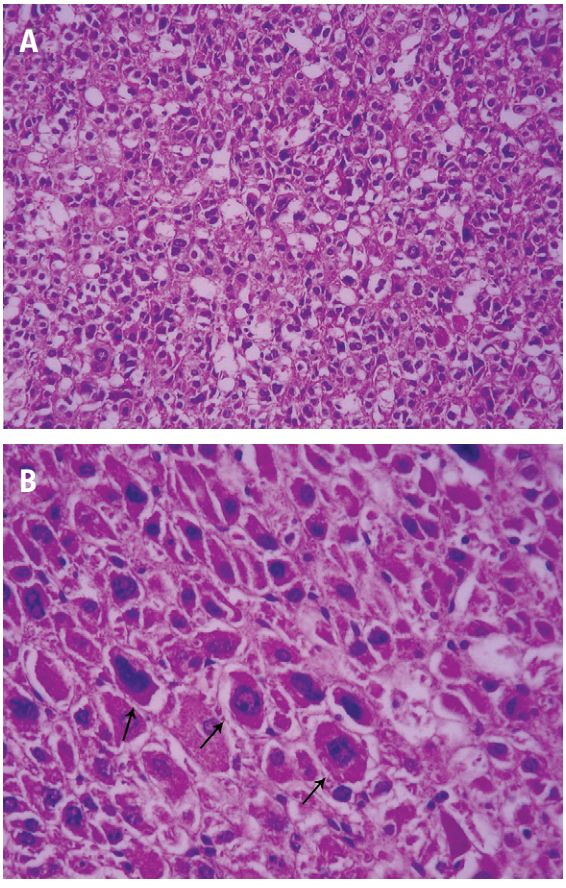

Figure 3. Microscopic section (hematoxylin & eosin stain) shows pleomorphic tumor cells with intensely eosinophilic cytoplasm and hyperchromatic bizarre nuclei (arrows): (A) × 100; (B) × 250.

Discussion

This rare case of virilizing ACC showed concordant uptake on NP-59 scintiscan. Our review of the English literature revealed only 10 previous reports of primary ACC with a concordant NP-59 imaging pattern, including three patients with Cushing's syndrome (one associated with hirsutism),[8–10] six patients with primary aldosteronism,[11–14] and one patient with increased urinary excretion of androsterone and DHEA[15] (Table).[16] All of these tumors secreted excess hormones biochemically and produced clinical endocrinologic symptoms and signs, and some were also described as being well differentiated on histologic examination of the resected tissues.[9–11,15] Most (9/11) of these tumors were found at a lower stage (≤ stage 2), and most (7/11) of the patients remained free of recurrence during the follow-up period after tumor resection. Thus, both the functional status of the tumor and the degree of differentiation of tumor cells appear to be important factors in determining visualization on NP-59 scintigraphy, with the degree of differentiation of tumor cells, i.e. grade of malignancy, probably being the more im-

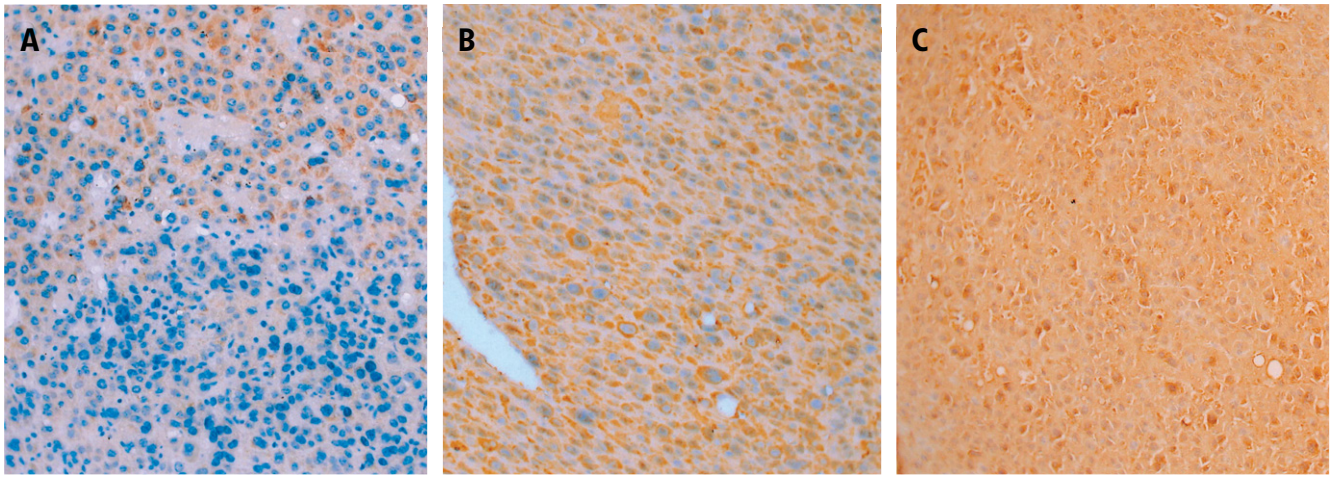

Figure 4. (A) Focal immunostaining to aldosterone (diaminobenzidine [DAB], brown, × 100). Differing from that of aldosterone, the immunoreactivity to both (B) testosterone and (C) DHEAS was diffuse and intense (DAB, brown, × 100).

portant factor. The findings in this case, a predominantly testosterone and DHEAS secreting virilizing ACC of relatively low grade malignancy (stage 2), which remained free of recurrence during 34 months of follow-up, support this hypothesis.

Hypertension and hypokalemia are the most common clinical features of primary aldosteronism. However, despite a high serum aldosterone level, our patient was normotensive and normokalemic, as has been reported in a previous case.[17] Since hypertension is usually followed by hypokalemia in the evolving course of primary aldosteronism, our patient might have been in the very early stage of primary aldosteronism, displaying no symptoms or signs of mineralocorticoid excess clinically, which is characteristic of the normokalemic type.[18]

Steroidogenesis in human ACC is unique, and has been described either as low efficiency steroid production or abnormal steroidogenesis.[19] In this case, extremely high plasma DHEAS and testo-

Table. NP-59 scan positive primary adrenocortical carcinomas reported in the English literature

Age/Sex	Hypersecretory state	Tumor size (cm)	Staging at presentation*	Postoperative survival	Reference #
30/F	Cushing's syndrome	8	2	Died at 9 mo	8
66/F	Cushing's syndrome	5	2	Alive at 21 mo	9
66/F	Cushing's syndrome (with hirsutism)	5	2	Alive at 66 mo	10
47/F	Primary aldosteronism	3	1	Alive at 32 mo	11
67/F	Primary aldosteronism	7	2	Alive at 17 mo	12
43/M	Primary aldosteronism	5	2	Alive at 18 mo	13
54/F	Primary aldosteronism	11	3	Alive at 6 mo	13
42/M	Primary aldosteronism	7	2	Alive at 35 mo	14
54/F	Primary aldosteronism	11	3	Alive at 2 mo	14
43/F	Incidentaloma, with elevated androsterone & DHEA excretion in urine	22	2	Died at 11 mo	15
17/F	Virilism, with increased testosterone, DHEAS & aldosterone secretion	11	2	Alive at 34 mo	Present case

**Staging: 1, < 5 cm; 2, > 5 cm and confined to the adrenal gland; 3, locoregional invasion or spread to local lymph nodes; and 4, distant metastasis.*[16]

sterone levels were documented, which were apparently responsible for clinical virilization of the patient. DHEAS is a well-known adrenal androgen produced exclusively by the adrenals, whereas only a minimal amount of testosterone is produced in normal adrenals.[20] It has been suggested that excess testosterone production in virilizing adrenocortical tumors derives mainly from peripheral conversion of adrenal androgens, including DHEA, DHEAS, delta(5)-androstenediol, and delta(4)-androstenedione.[21] In this case, immunohistochemical staining demonstrated that testosterone could be produced directly from ACC cells. This finding is in accordance with a previous case report in which the ACC cells were capable of synthesizing testosterone.[22] The activity of 17β-hydroxysteroid dehydrogenase, the enzyme responsible for converting androstenedione to testosterone, has been shown to be 50-fold higher in virilizing adrenal adenomas than in normal adrenals.[23] However, its activity in virilizing ACCs has not yet been studied; therefore, whether a similar mechanism exists and is responsible for the observed increased secretion of testosterone in virilizing ACCs remains to be determined. Further research regarding the activity or expression of 17β-hydroxysteroid dehydrogenase on ACCs is needed to provide insight into the steroidogenic pathways of these tumors.

In this case, immunostaining to aldosterone appeared to be more intense in tumor cells with less nuclear atypia and with a trabecular or cord-like pattern. This histologic finding has been described as a characteristic of functioning ACCs.[24] However, since there is much structural overlap between functioning and nonfunctioning tumors, tumor functionality cannot be predicted based on histology alone.[24] In contrast to that of aldosterone, immunostaining to DHEAS and testosterone was diffuse and intense even in areas of nuclear pleomorphism and of sarcoma-like pattern. This discrepancy may reflect the diversity and complexity of the steroidogenic pathways of ACCs.

In summary, this case of virilization due to a large ACC exhibited intense unilateral uptake on NP-59 adrenal scan. The tumor was shown to be capable of producing a mixture of steroids, including testosterone, DHEAS and aldosterone, both *in vivo* and *in vitro*. This case illustrates the potential pitfall of assuming that all ACCs are unable to uptake sufficient radiotracer for imaging on NP-59 scanning. Visualization of an adrenal tumor on NP-59 scintiscan cannot exclude the possibility of malignancy.

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